A unique case of hybrid SEF-LGFMS with a EWSR1-CREB3L1 Fusion and robotic-assisted bronchoscopy in an 11-year-old

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Abbreviations:

CT	Computed Tomography
DLCO	Diffusing Capacity for Carbon Monoxide
EWSR1-CREB3L1	Ewing sarcoma breakpoint region 1-cAMP-responsive element binding protein 3-like 1
FUS (gene)	Fused in Sarcoma (gene)
RLL	Right lower lobe
ROSE	Rapid on-site evaluation
SEF-LGFMS	Sclerosing epithelioid fibrosarcoma (SEF)-low grade fibromyxoid sarcoma
VA	Alveolar volume
WES/WTS	Sema4 whole exome sequencing / whole transcriptome sequencing

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To the editor,

Primary lung malignancies in the pediatric population are rare at 0.049 per 100,000 individuals, with a histological distribution unique to the pediatric population (1, 2). Here we present a novel case of a child who presented with hemoptysis that safely underwent robotic assisted flexible bronchoscopy and was diagnosed with a tumor not previously reported in the literature with the lung as primary site: a hybrid sclerosing epithelioid fibrosarcoma (SEF)-low grade fibromyxoid sarcoma (LGFMS), with Ewing sarcoma breakpoint region 1 (EWSR1)/cAMP-responsive element binding protein 3-like 1 (CREB3L1) fusion mutation.

EWSR1/CREB3L1 are the most frequent fusion mutations in SEF, composing 80-90% of cases, while FUS/CREB3L1 and FUS/CREB3L2 gene fusions are more common in hybrid or LGFMS (8). EWSR1 is an RNA binding protein that functions in maintenance of genomic integrity and CREB3L1 is a transcription factor implicated in cancer cell migration and invasion (3, 4). EWSR1 belongs to the same family of RNA binding proteins as Fused in Sarcoma (FUS) gene, and mutations in both drive soft tissue tumors, though mutation frequency varies by sarcoma type (3). SEF is associated with a more aggressive clinical course than LGFMS, though differences in clinical presentation between patients with EWSR1-CREB3L1 fusions and FUS-CREB3L1 fusions remain an active area of research. SEF, LGFMS, and hybrid tumors are all rare in the pediatric population (5).

An 11-year-old female with no significant medical history presented to the emergency department with cough, shortness of breath and 3 episodes of bright red hemoptysis for 1 day. A chest x-ray showed a round, well-demarcated 4.1 cm mass in the right lower lung (Figure 1). A computed tomography (CT) chest revealed a 4.9 x 3.0 cm mass in the right lower lobe with coarse calcification (Figure 2), suggestive of a pulmonary hamartoma.

The patient underwent flexible bronchoscopy with transbronchial needle aspiration guided by radial ultrasound. Rapid on-site evaluation (ROSE) did not show adequate specimens. The case was converted to robotic-guided bronchoscopy; transbronchial needle aspiration and transbronchial biopsies of the right lower lobe (RLL) mass were successfully obtained. Surgical pathology showed fragments of fibromyxoid stroma possibly consistent with hamartoma but not conclusive. Patient then underwent a RLL lobectomy and pathology revealed a hybrid SEF-LGFMS, with genetic sequencing [Sema4 whole exome sequencing (WES)/ whole transcriptome sequencing (WTS)] demonstrating an EWSR1-CREB3L1 fusion gene. Background lung demonstrated emphysema and hemorrhage; bronchial and vascular markers were negative for tumor.

The patient underwent staging scans, negative for metastasis. Pulmonary function testing demonstrated low diffusing capacity for carbon monoxide (DLCO), yet normal DLCO/alveolar volume (VA) and total lung capacity. After surgical resection, the patient has been in complete remission for 12 months.

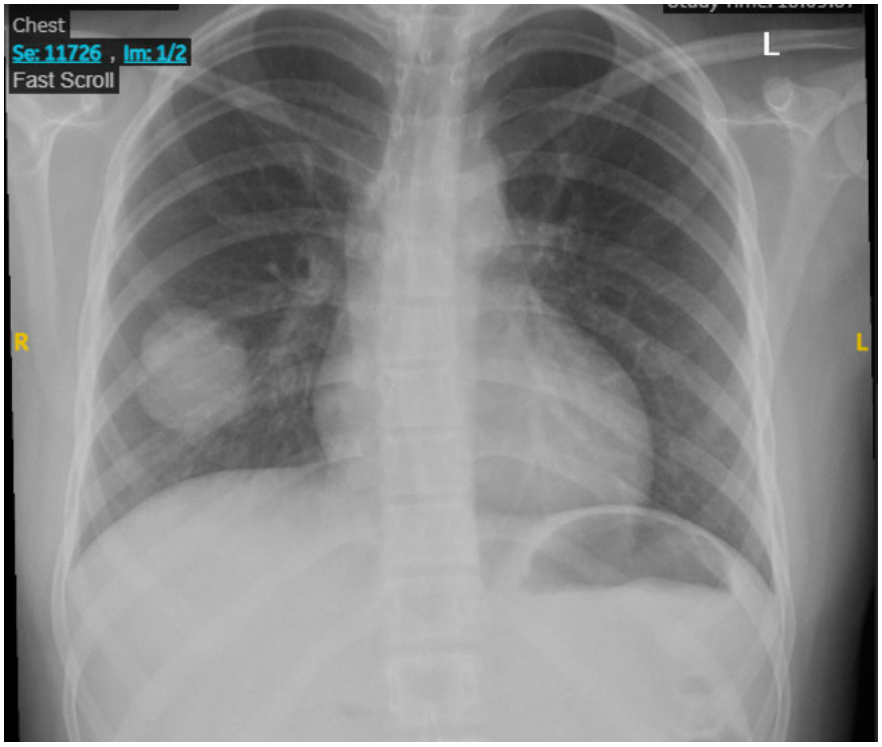

Figure 1. *Initial chest x-ray showed a rounded relatively well demarcated radiodensity measuring 4.1 cm in the right lower lobe of the lung. It was thought to represent a neoplastic growth versus a congenital anomaly/variant structure. Pulmonary hemorrhage is felt to be less likely.*

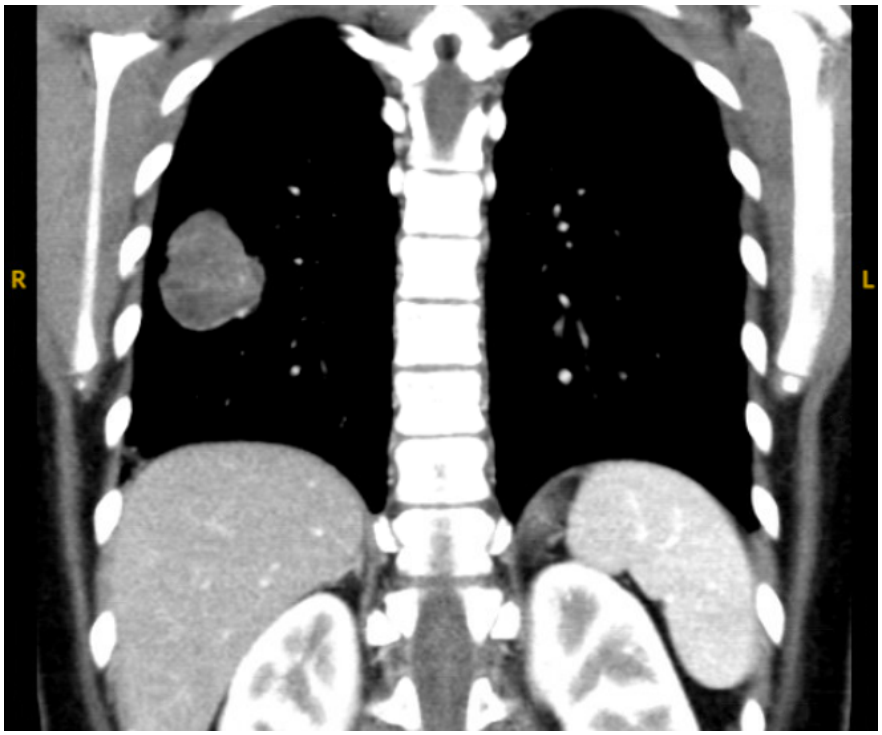

Figure 2 . *Initial chest CT revealed a 4.9 x 3.0 cm mass in the right lower lobe with coarse calcification which most likely corresponds to a pulmonary hamartoma. There are additional scattered ground glass opacities in the bilateral lung fields, right greater than left, which most likely correspond to viral or atypical pneumonia, though pulmonary hemorrhage could not be fully excluded in the setting of hemoptysis.*

DISCUSSION

To this date, this hybrid SEF-LGFMS tumor with an EWSR1/CREB3L1 fusion has not been described in the literature as a primary lung neoplasm. Only one other EWSR1/CREB3L1 hybrid SEF-LGMS tumor has been reported, a 10-year-old primary renal tumor (7). The patient presented with widespread metastases, underwent biopsy and subsequent palliative chemotherapy; the patient died of metastatic disease 12 months after the diagnosis.

In contrast, the EWSR1/CREB3L1 gene fusion has been observed in 80-90% of SEF (a rare soft-tissue sarcoma) cases (8). The youngest patient reported with SEF and an EWSR1-CREB3L1 mutation was a 3-year-old who presented with numerous lung and bone metastases (8). In a case series of four pediatric patients with SEF in deep soft tissues of the trunk harboring EWSR1-CREB3L1 mutations, one patient did not receive further treatment and died 17 months after diagnosis, two remained disease-free post-surgery, and one remained disease-free 22 months following radiation and multiple chemotherapy cycles (9). A review of 51 SEF cases (4/51 pediatric) found that 10% of primary SEF tumors occurred in the lung, while 42.1% of metastatic tumors were found in the lung/pleura (10).

LGFMS is an indolent tumor with metastatic potential and has only been reported in 33 pediatric patients. As with hybrid SEF-LGFMS tumors, most LGFMS cases display FUS-CREB3L2 mutations; only four case reports thus far demonstrate EWSR1-CREB3L1 fusion mutations in LGFMS (with primary tumors of the orbit, lower leg, thigh, and kidney) (11,12). Of the two pediatric patients with EWSR1-CREB3L1 LGFMS, one presented with a subcutaneous nodule on the lower leg and is disease-free 12 months after excision; the other presented with a primary renal solid tumor and was disease-free 18 months post-surgical excision of solely the encapsulated mass (12).

This is only the second reported case of the use of robotic bronchoscopy in a pediatric patient. Though a specimen was obtained safely in our patient, it was not diagnostic, and an additional specimen was obtained surgically (13). There is a need for less invasive sampling of lung lesions in the pediatric population. Clinicians choose between surgical sampling and less often, flexible bronchoscopy with endobronchial or transbronchial biopsy. Robotic assisted bronchoscopy has recently joined this list as an option, due to its stability, adjustability, and peripheral visualization (14).

This unique case provides insight into the clinical and pathologic presentation of a EWSR1-CREB3L1 driven primary lung hybrid SEF- LGFMS, further broadening the molecular spectrum of pediatric lung tumors.

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